PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 277/06, A61K 31/425 — A1

(11) International Publication Number: **WO 99/48879**

(43) International Publication Date: 30 September 1999 (30.09.99)

(21) International Application Number: PCT/GB99/00920

(22) International Filing Date: 24 March 1999 (24.03.99)

(30) Priority Data:

9806309.2	24 March 1998 (24.03.98)	GB
9811157.8	22 May 1998 (22.05.98)	GB

(71) Applicant *(for all designated States except US)*: CELLTECH THERAPEUTICS LIMITED [GB/GB]; 216 Bath Road, Slough, Berkshire SL1 4EN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: ARCHIBALD, Sarah, Catherine [GB/GB]; 5 College Glen, Maidenhead, Berkshire SL6 6BL (GB). HEAD, John, Clifford [GB/GB]; 4 Dorchester Close, Maidenhead, Berkshire SL6 6RX (GB). WARRELLOW, Graham, John [GB/GB]; 4 Wieland Road, Oakside, Northwood, Middlesex HA6 3QU (GB). PORTER, John, Robert [GB/GB]; 5 Farm Place, Henton, Chinnor, Oxfordshire 0X9 4AD (GB).

(74) Agent: MERCER, Christopher, Paul; Carpmaels & Ransford, 43 Bloomsbury Square, London WC1A 2RA (GB).

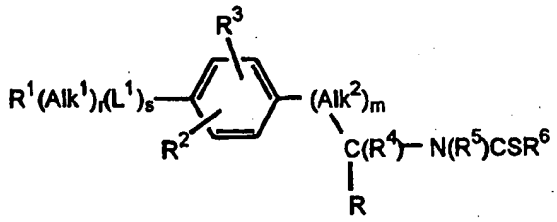
(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: THIOCARBOXAMIDE DERIVATIVES AND THEIR USE AS INHIBITORS OF ALPHA-4 INTEGRINS



(1)

(57) Abstract

Compounds of formula (1), wherein R^1 is a hydrogen atom or an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group; Alk^1 is an optionally substituted aliphatic or heteroaliphatic chain; L^1 is a linker atom or group; r and s is each zero or an integer 1; R^2 and R^3, which may be the same or different, is each a hydrogen or halogen atom or a straight or branched alkyl, haloalkyl, alkoxy, haloalkoxy, hydroxyl or nitro group; Alk^2 is a straight or branched alkylene chain; m is zero or an integer 1; R^4 is a hydrogen atom or a methyl group; R^5 is a hydrogen atom or a straight or branched alkyl group; R^6 is a group $-(CH_2)_tR^7$ in which t is zero or the integer 1 and R^7 is an optionally substituted polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group; R is a carboxylic acid ($-CO_2H$) or a derivative thereof; and the salts, solvates and hydrates thereof are described. The compounds are able to inhibit the binding of alpha 4 integrins to their ligands and are of use in the prophylaxis and treatment of immune or inflammatory disorders.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

THIOCARBOXAMIDE DERIVATIVES AND THEIR USE AS INHIBITORS OF ALPHA-4 INTEGRINS

This invention relates to a series of thioamides, to compositions containing them, to processes for their preparation, and to their use in medicine.

Over the last few years it has become increasingly clear that the physical interaction of inflammatory leukocytes with each other and other cells of the body plays an important role in regulating immune and inflammatory responses [Springer, T A. Nature, 346, 425, (1990); Springer, T. A. Cell 76, 301, (1994)]. Many of these interactions are mediated by specific cell surface molecules collectively referred to as cell adhesion molecules.

The adhesion molecules have been sub-divided into different groups on the basis of their structure. One family of adhesion molecules which is believed to play a particularly important role in regulating immune and inflammatory responses is the integrin family. This family of cell surface glycoproteins has a typical non-covalently linked heterodimer structure. At least 14 different integrin alpha chains and 8 different integrin beta chains have been identified [Sonnenberg, A. Current Topics in Microbiology and Immunology, 184, 7, (1993)]. The members of the family are typically named according to their heterodimer composition although trivial nomenclature is widespread in this field. Thus the integrin termed $\alpha 4\beta 1$ consists of the integrin alpha 4 chain associated with the integrin beta 1 chain, but is also widely referred to as Very Late Antigen 4 or VLA4. Not all of the potential pairings of integrin alpha and beta chains have yet been observed in nature and the integrin family has been subdivided into a number of subgroups based on the pairings that have been recognised [Sonnenberg, A. *ibid*].

The importance of cell adhesion molecules in human leukocyte function has been further highlighted by a genetic deficiency disease called Leukocyte Adhesion Deficiency (LAD) in which one of the families of leukocyte integrins is not expressed [Marlin, S. D. *et al* J. Exp. Med. 164, 855 (1986)]. Patients with this disease have a reduced ability to recruit

leukocytes to inflammatory sites and suffer recurrent infections which in extreme cases may be fatal.

The potential to modify adhesion molecule function in such a way as to beneficially modulate immune and inflammatory responses has been extensively investigated in animal models using specific monoclonal antibodies that block various functions of these molecules [e.g. Issekutz, T. B. J. Immunol. 3394, (1992); Li, Z. *et al* Am. J. Physiol. 263, L723, (1992); Binns, R. M. *et al* J. Immunol. 157, 4094, (1996)]. A number of monoclonal antibodies which block adhesion molecule function are currently being investigated for their therapeutic potential in human disease.

One particular integrin subgroup of interest involves the α4 chain which can pair with two different beta chains β1 and β7 [Sonnenberg, A. *ibid*]. The α4β1 pairing occurs on many circulating leukocytes (for example lymphocytes, monocytes and eosinophils) although it is absent or only present at low levels on circulating neutrophils. α4β1 binds to an adhesion molecule (Vascular Cell Adhesion Molecule-1 also known as VCAM-1) frequently up-regulated on endothelial cells at sites of inflammation [Osborne, L. Cell, 62, 3, (1990)]. The molecule has also been shown to bind to at least three sites in the matrix molecule fibronectin [Humphries, M. J. *et al*. Ciba Foundation Symposium, 189, 177, (1995)]. Based on data obtained with monoclonal antibodies in animal models it is believed that the interaction between α4β1 and ligands on other cells and the extracellular matrix plays an important role in leukocyte migration and activation [Yednock, T. A. *et al*, Nature, 356, 63, (1992); Podolsky, D. K. *et al*. J. Clin. Invest. 92, 373, (1993); Abraham, W. M. *et al*. J. Clin. Invest. 93, 776, (1994)].

The integrin generated by the pairing of α4 and β7 has been termed LPAM-1 [Holzmann, B and Weissman, I. EMBO J. 8, 1735, (1989)] and like α4β1, binds to VCAM-1 and fibronectin. In addition, α4β7 binds to an adhesion moleculebelieved to be involved in the homing of leukocytes to mucosal tissue termed MAdCAM-1 [Berlin, C. *et al*, Cell, 74, 185, (1993)]. The interaction between α4β7 and MAdCAM-1 may also be important at

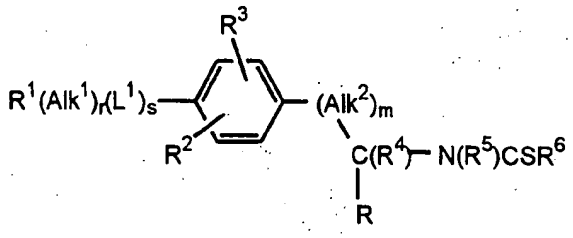
sites of inflammation outside of mucosal tissue [Yang, X-D. *et al*, PNAS, 91, 12604 (1994)].

Regions of the peptide sequence recognised by α4β1 and α4β7 when they bind to their ligands have been identified. α4β1 seems to recognise LDV, IDA or REDV peptide sequences in fibronectin and a QIDSP sequence in VCAM-1 [Humphries, M. J. *et al*, *ibid*] whilst α4β7 recognises a LDT sequence in MAdCAM-1 [Briskin, M. J. *et al*, J. Immunol. 156, 719, (1996)]. There have been several reports of inhibitors of these interactions being designed from modifications of these short peptide sequences [Cardarelli, P. M. *et al* J. Biol. Chem. 269, 18668, (1994); Shroff, H. N. Bioorganic. Med. Chem. Lett. 6, 2495, (1996); Vanderslice, P. J. Immunol. 158, 1710, (1997)]. It has also been reported that a short peptide sequence derived from the α4β1 binding site in fibronectin can inhibit a contact hypersensitivity reaction in a trinitrochlorobenzene sensitised mouse [Ferguson, T. A. *et al*, PNAS 88, 8072, (1991)].

Since the alpha 4 subgroup of integrins are predominantly expressed on leukocytes their inhibition can be expected to be beneficial in a number of immune or inflammatory disease states. However, because of the ubiquitous distribution and wide range of functions performed by other members of the integrin family it is very important to be able to identify selective inhibitors of the alpha 4 subgroup.

We have now found a group of compounds which are potent and selective inhibitors of α4 integrins. Members of the group are able to inhibit α4 integrins such as α4β1 and/or α4β7 at concentrations at which they generally have no or minimal inhibitory action on α integrins of other subgroups. The compounds are thus of use in medicine, for example in the prophylaxis and treatment of immune or inflammatory disorders as described hereinafter.

Thus according to one aspect of the invention we provide a compound of formula (1)



(1)

wherein

R^1 is a hydrogen atom or an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;

Alk^1 is an optionally substituted aliphatic or heteroaliphatic chain;

L^1 is a linker atom or group;

r and s is each zero or an integer 1;

R^2 and R^3, which may be the same or different, is each a hydrogen or halogen atom or a straight or branched alkyl, haloalkyl, alkoxy, haloalkoxy, hydroxyl or nitro group;

Alk^2 is a straight or branched alkylene chain;

m is zero or an integer 1;

R^4 is a hydrogen atom or a methyl group;

R^5 is a hydrogen atom or a straight or branched alkyl group;

R^6 is a group $-(CH_2)_tR^7$ in which t is zero or the integer 1 and R^7 is an optionally substituted polycycloaliphatic, heterocycloaliphatic, polyhetero-cycloaliphatic, aromatic or heteroaromatic group;

R is a carboxylic acid ($-CO_2H$) or a derivative thereof;

and the salts, solvates and hydrates thereof.

It will be appreciated that compounds of formula (1) may have one or more chiral centres. Where one or more chiral centres is present, enantiomers or diastereomers may exist, and the invention is to be understood to extend to all such enantiomers, diasteromers and mixtures thereof, including racemates. Formula (1) and the formulae hereinafter are intended to represent all individual isomers and mixtures thereof, unless stated or shown otherwise.

In the compounds of formula (1), derivatives of the carboxylic acid group R include carboxylic acid esters and amides. Particular esters and amides include those $-CO_2Alk^5$, $-CONH_2$, $-CONHR^{12}$ and $-CON[R^{12}]_2$ groups described below in relation to the group R^7.

Alk^2 in the compounds of the invention may be for example a straight or branched C_{1-3}alkylene chain. Particular examples include $-CH_2-$, $-CH(CH_3)-$ and $-(CH_2)_2-$.

When R^5 in the compounds of formula (1) is a straight or branched alkyl group it may be a straight or branched C_{1-6}alkyl group, e.g. a C_{1-3}alkyl group such as a methyl or ethyl group.

When in the compounds of the invention L^1 is present as a linker atom or group it may be any divalent linking atom or group. Particular examples include -O- or -S- atoms or -C(O)-, -C(O)O-, -C(S)-, -S(O)-, $-S(O)_2-$, $-N(R^8)-$ [where R^8 is a hydrogen atom or an optionally substituted alkyl group], $-CON(R^8)-$, $-OC(O)N(R^8)-$, $-CSN(R^8)-$, $-N(R^8)CO-$, $-N(R^8)C(O)O-$, $-N(R^8)CS-$, $-S(O)_2N(R^8)-$, $-N(R^8)S(O)_2-$, $-N(R^8)CSN(R^8)-$, -or $-N(R^8)SO_2N(R^8)-$ groups. Where the linker group contains two R^8 substituents, these may be the same or different.

When Alk^1 in compounds of formula (1) is an optionally substituted aliphatic chain it may be an optionally substituted C_{1-10} aliphatic chain. Particular examples include optionally substituted straight or branched chain C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl chains.

Heteroaliphatic chains represented by Alk^1 include the aliphatic chains just described but with each chain additionally containing one, two, three or four heteroatoms or heteroatom-containing groups. Particular heteroatoms or groups include atoms or groups L^2 where L^2 is as defined above for L^1 when L^1 is a linker atom or group. Each L^2 atom or group may interrupt the aliphatic chain, or may be positioned at its terminal carbon atom to connect the chain to an adjoining atom or group.

Particular examples of aliphatic chains represented by Alk^1 include optionally substituted $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2$, $-(CH_2)_2CH_2-$, $-CH(CH_3)CH_2-$, $-(CH_2)_3CH_2-$, $-CH(CH_3)CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, $-C(CH_3)_2CH_2-$, $-(CH_2)_4CH_2-$, $-(CH_2)_5CH_2-$, $-CHCH-$, $-CHCHCH_2-$, $-CH_2CHCH-$, $-CHCHCH_2CH_2-$, $-CH_2CHCHCH_2-$, $-(CH_2)_2CHCH-$, $-CC-$, $-CCCH_2-$, $-CH_2CC-$, $-CCCH_2CH_2-$, $-CH_2CCCH_2-$, or $-(CH_2)_2CC-$ chains. Where appropriate each of said chains may be optionally interrupted by one or two atoms and/or groups L^2 to form an optionally substituted heteroaliphatic chain. Particular examples include optionally substituted $-L^2CH_2-$, $-CH_2L^2CH_2-$, $-L^2(CH_2)_2-$, $-CH_2L^2(CH_2)_2-$, $-(CH_2)_2L^2CH_2-$, $-L^2(CH_2)_3-$ and $-(CH_2)_2L^2(CH_2)_2-$ chains.

The optional substituents which may be present on aliphatic or heteroaliphatic chains represented by Alk^1 include one, two, three or more substituents where each substituent may be the same or different and is selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or C_{1-6}alkoxy, e.g. methoxy or ethoxy, thiol, C_{1-6}alkylthio e.g. methylthio or ethylthio, amino or substituted amino groups. Substituted amino groups include $-NHR^9$ and $-N(R^9)_2$ groups where R^9 is an optionally substituted straight or branched alkyl group as defined above for R^5. Where two R^9 groups are present these may be the same or different. Particular examples of substituted chains represented by Alk^1 include those specific chains just described substituted by one, two, or three halogen atoms such as fluorine atoms, for example chains of the type $-CH(CF_3)-$, $-C(CF_3)_2-$ $-CH_2CH(CF_3)-$, $-CH_2C(CF_3)_2-$, $-CH(CF_3)-$ and $-C(CF_3)_2CH_2$.

Optionally substituted heterocycloaliphatic groups represented by R^7 include optionally substituted C_{3-10}heterocycloaliphatic groups. Particular examples include optionally substituted C_{3-10}heterocycloalkyl, e.g. C_{3-7} heterocycloalkyl or C_{3-10}heterocycloalkenyl, e.g. C_{3-7}hetercycloalkenyl groups, each of said groups containing one, two, three or four heteroatoms or heteroatom-containing groups L^2 as just defined.

Optionally substituted polycycloaliphatic groups represented by R^7 include optionally substitued C_{7-10} bi- or tricycloalkyl or C_{7-10}bi- or tricycloalkenyl

groups. Optionally substituted polyheterocycloaliphatic groups represented by R^7 include the optionally substituted polycycloalkyl groups just described, but with each group additionally containing one, two, three or four L^3 atoms or groups.

Particular examples of R^7 polycycloaliphatic, heterocycloaliphatic and polyheterocycloaliphatic groups include optionally substituted adamantyl, norbornyl, norbornenyl, tetrahydrofuranyl, pyrroline, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, pyrrolidinone, oxazolidinyl, oxazolidinone, dioxolanyl, e.g. 1,3-dioxolanyl, imidazolinyl, e.g. 2-imidazolinyl, imidazolidinyl, pyrazolinyl, e.g. 2-pyrazolinyl, pyrazolidinyl, pyranyl, e.g. 2- or 4-pyranyl, piperidinyl, piperidinone, 1,4-dioxanyl, morpholinyl, morpholinone, 1,4-dithianyl, thiomorpholinyl, piperazinyl, 1,3,5-trithianyl, oxazinyl, e.g. 2H-1,3-, 6H-1,3-, 6H-1,2-, 2H-1,2- or 4H-1,4- oxazinyl, 1,2,5-oxathiazinyl, isoxazinyl, e.g. o- or p-isoxazinyl, oxathiazinyl, e.g. 1,2,5 or 1,2,6-oxathiazinyl, or 1,3,5,-oxadiazinyl groups.

The optional substituents which may be present on the R^7 polycyclo-aliphatic, heterocycloaliphatic or polyheterocycloaliphatic groups include one, two, three or more substituents selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or hydroxyl, C_{1-6}alkoxy, e.g. methoxy or ethoxy, thiol, C_{1-6}alkylthio e.g. methylthio or ethylthio, amino or substituted amino groups. Substituted amino groups include $-NHR^9$ and $-N(R^9)_2$ groups where R^9 is as defined above. Additionally, when R^7 is a heterocycloaliphatic group containing one or more nitrogen atoms each nitrogen atom may be optionally substituted by a group $-(L^3)_p(Alk^3)_qR^{10}$ in which L^3 is $-C(O)-$, $-C(O)O-$, $-C(S)-$, $-S(O)_2-$, $-CON(R^8)-$, $-CSN(R^8)-$, $-SON(R^8)-$ or $SO_2N(R^8)-$; p is zero or an integer 1; Alk^3 is an optionally substituted aliphatic or heteroaliphatic chain; q is zero or an integer 1; and R^{10} is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, polycycloaliphatic, polyheterocyclo-aliphatic, aromatic or heteroaromatic group.

Optionally substituted aliphatic or heteroaliphatic chains represented by Alk^3 include those optionally substituted chains described above for Alk^1.

Optionally substituted cycloaliphatic, heterocycloaliphatic, polycyloaliphatic or polyheterocycloaliphatic groups represented by R^{10} include those groups just described for R^7. Optional substituents which may be present on these groups include those described above in relation to Alk^1 aliphatic and heteroaliphatic chains.

Optionally substituted aromatic or heteroaromatic groups represented by R^{10} include those aromatic and heteroaromatic groups generally and specifically described below for R^7.

In the compounds of formula (1), optionally substituted aromatic groups represented by the group R^7 and/or R^{10} nclude for example optionally substituted monocyclic or bicyclic fused ring C_{6-12} aromatic groups, such as optionally substituted phenyl, 1- or 2-naphthyl, 1- or 2-tetrahydro-naphthyl, indanyl or indenyl groups .

Optionally substituted heteroaromatic groups, represented by the group R^7 and/or R^{10} in compounds of formula (1) include for example optionally substituted C_{1-9} heteroaromatic groups containing for example one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, the heteroaromatic groups may be for example monocyclic or bicyclic fused ring heteroaromatic groups. Monocyclic heteroaromatic groups include for example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Bicyclic heteroaromatic groups include for example nine- to thirteen-membered fused-ring heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

Particular examples of heteroaromatic groups of these types include optionally substituted pyrrolyl, furyl, thienyl, imidazolyl, N-methylimidazolyl, N-ethylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazole, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]benzofuryl, isobenzofuryl, benzothienyl, benzo-

triazolyl, indolyl, isoindolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, benzopyranyl, [3,4-dihydro]benzopyranyl, quinazolinyl, naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolinyl, isoquinolinyl, tetrazolyl, 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, and imidyl, e.g. succinimidyl, phthalimidyl, or naphthalimidyl such as 1,8-naphthalimidyl.

Optional substituents which may be present on the aromatic or heteroaromatic groups represented by R^7 and/or R^{10} include one, two, three or more substituents, each selected from an atom or group R^{11} in which R^{11} is $-R^{11a}$ or $-Alk^4(R^{11a})_m$, where R^{11a} is a halogen atom, or an amino ($-NH_2$), substituted amino, nitro, cyano, amidino, hydroxyl ($-OH$), substituted hydroxyl, formyl, carboxyl ($-CO_2H$), esterified carboxyl, thiol ($-SH$), substituted thiol, $-COR^{12}$ [where R^{12} is an $-Alk^4(R^{11a})_m$, aryl or heteroaryl group], $-CSR^{12}$, $-SO_3H$, $-SO_2R^{12}$, $-SO_2NH_2$, $-SO_2NHR^{12}$ $SO_2N(R^{12})_2$, $-CONH_2$, $-CSNH_2$, $-CONHR^{12}$, $-CSNHR^{12}$, $-CON[R^{12}]_2$, $-CSN(R^{12})_2$, $-N(R^8)SO_2R^{12}$, $-N(SO_2R^{12})_2$, $-N(R^8)SO_2NH_2$, $-N(R^8)SO_2NHR^{12}$, $-N(R^8)SO_2N(R^{12})_2$, $-N(R^8)COR^{12}$, $-N(R^8)CON(R^{12})_2$, $-N(R^8)CSN(R^{12})_2$, $-N(R^8)CSR^{12}$, $-N(R^8)C(O)OR^{12}$, $-SO_2NHet^1$ [where $-NHet^1$ is an optionally substituted C_{5-7}cyclicamino group optionally containing one or more other -O- or -S- atoms or $-N(R^8)$-, -C(O)- or -C(S)- groups], $-CONHet^1$, $-CSNHet^1$, $-N(R^8)SO_2NHet^1$, $-N(R^8)CONHet^1$, $-N(R^8)CSNHet^1$, $-SO_2N(R^8)Het^2$ [where Het^2 is an optionally substituted monocyclic C_{5-7}carbocyclic group optionally containing one or more -O- or -S- atoms or $-N(R^8)$-, -C(O)- or -C(S)- groups], $-CON(R^8)Het^2$, $-CSN(R^8)Het^2$, $-N(R^8)CON(R^8)Het^2$, $-N(R^8)CSN(R^8)Het^2$, aryl or heteroaryl group; Alk^4 is a straight or branched C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6}alkynylene chain, optionally interrupted by one, two or three -O- or -S- atoms or $-S(O)_n$ [where n is an integer 1 or 2] or $-N(R^{13})$- groups [where R^{13} is a hydrogen atom or C_{1-6}alkyl, e.g. methyl or ethyl group]; and m is zero or an integer 1, 2 or 3. It will be appreciated that when two R^8 or R^{12} groups are present in one of the above substituents, the R^8 or R^{12} groups may be the same or different.

When in the group $-Alk^4(R^{11a})_m$ m is an integer 1, 2 or 3, it is to be understood that the substituent or substituents R^{11a} may be present on

any suitable carbon atom in -Alk^4-. Where more than one R^{11a} substituent is present these may be the same or different and may be present on the same or different atom in -Alk^4-. Clearly, when m is zero and no substituent R^{11a} is present the alkylene, alkenylene or alkynylene chain represented by Alk^4 becomes an alkyl, alkenyl or alkynyl group.

When R^{11a} is a substituted amino group it may be for example a group -NHR^{12} [where R^{12} is as defined above] or a group -$N(R^{12})_2$ wherein each R^{12} group is the same or different.

When R^{11a} is a halogen atom it may be for example a fluorine, chlorine, bromine, or iodine atom.

When R^{11a} is a substituted hydroxyl or substituted thiol group it may be for example a group -OR^{12} or a -SR^{12} or -$SC(=NH)NH_2$ group respectively.

Esterified carboxyl groups represented by the group R^{11a} include groups of formula -CO_2Alk^5 wherein Alk^5 is a straight or branched, optionally substituted C_{1-8}alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; a $C_{6-12}aryl C_{1-8}$alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; a C_{6-12}aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a $C_{6-12}aryloxy C_{1-8}$alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, 1-naphthyl-oxymethyl, or 2-naphthyloxymethyl group; an optionally substituted $C_{1-8}alkanoyloxy C_{1-8}$alkyl group, such as a pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; or a $C_{6-12}aroyloxy C_{1-8}$alkyl group such as an optionally substituted benzoyloxyethyl or benzoyloxypropyl group. Optional substituents present on the Alk^5 group include R^{11a} substituents described above.

When Alk^4 is present in or as a substituent it may be for example a methylene, ethylene, n-propylene, i-propylene, n-butylene, i-butylene, s-butylene, t-butylene, ethenylene, 2-propenylene, 2-butenylene, 3-butenylene, ethynylene, 2-propynylene, 2-butynylene or 3-butynylene

chain, optionally interrupted by one, two, or three -O- or -S-, atoms or -S(O)-, -S(O)$_2$- or -N(R^8)- groups.

Aryl or heteroaryl groups represented by the groups R^{11a} or R^{12} include mono- or bicyclic optionally substituted C_{6-12} aromatic or C_{1-9} heteroaromatic groups as described above for the group R^7. The aromatic and heteroaromatic groups may be attached to the remainder of the compound of formula (1) by any carbon or hetero e.g. nitrogen atom as appropriate.

When -NHet^1 or -Het^2 forms part of a substituent R^7 each may be for example an optionally substituted pyrrolidinyl, pyrazolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, piperidinyl or thiazolidinyl group. Additionally Het^2 may represent for example, an optionally substituted cyclopentyl or cyclohexyl group. Optional substituents which may be present on -NHet^1 or -Het^2 include those substituents described above in relation to Alk^1 chains.

Particularly useful atoms or groups represented by R^{11} include fluorine, chlorine, bromine or iodine atoms, or C_{1-6}alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl, optionally substituted phenyl, pyridyl, pyrrolyl, furyl, thiazolyl, or thienyl, C_{1-6}alkylamino, e.g. methylamino or ethylamino, C_{1-6}hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, carboxyC_{1-6}alkyl, e.g. carboxyethyl, C_{1-6}alkylthio e.g. methylthio or ethylthio, carboxyC_{1-6}alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxypropylthio, C_{1-6}alkoxy, e.g. methoxy or ethoxy, hydroxyC_{1-6}alkoxy, e.g. 2-hydroxyethoxy, optionally substituted phenoxy, pyridyloxy, thiazolyoxy, phenylthio or pyridylthio, C_{5-7}cycloalkoxy, e.g. cyclopentyloxy, haloC_{1-6}alkyl, e.g. trifluoromethyl, haloC_{1-6}alkoxy, e.g. trifluoromethoxy, C_{1-6}alkylamino, e.g. methylamino or ethylamino, amino (-NH_2), aminoC_{1-6}alkyl, e.g. aminomethyl or aminoethyl, C_{1-6}dialkylamino, e.g. dimethylamino or diethylamino, C_{1-6}alkylaminoC_{1-6}alkyl, e.g. ethylaminoethyl, C_{1-6}dialkylaminoC_{1-6}alkyl, e.g. diethylaminoethyl, aminoC_{1-6}alkoxy, e.g. aminoethoxy, C_{1-6}alkylaminoC_{1-6}alkoxy, e.g. methylaminoethoxy, C_{1-6}dialkylaminoC_{1-6}alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy, isopropylaminoethoxy, or dimethylaminopropoxy, imido, such as

phthalimido or naphthalimido, e.g. 1,8-naphthalimido, nitro, cyano, amidino, hydroxyl (-OH), formyl [HC(O)-], carboxyl (-CO_2H), -CO_2Alk^5 [where Alk^5 is as defined above], C_{1-6} alkanoyl e.g. acetyl, optionally substituted benzoyl, thiol (-SH), thioC_{1-6}alkyl, e.g. thiomethyl or thioethyl, -SC(=NH)NH_2, sulphonyl (-SO_3H), C_{1-6}alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl (-SO_2NH_2), C_{1-6}alkylaminosulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl, C_{1-6}dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, phenylaminosulphonyl, carboxamido (-$CONH_2$), C_{1-6}alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C_{1-6}dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, aminoC_{1-6}alkylaminocarbonyl, e.g. aminoethylaminocarbonyl, C_{1-6}dialkylaminoC_{1-6}alkylaminocarbonyl, e.g. diethylaminoethylaminocarbonyl, aminocarbonylamino, C_{1-6}alkylaminocarbonylamino, e.g. methylaminocarbonylamino or ethylaminocarbonylamino, C_{1-6}dialkylaminocarbonylamino, e.g. dimethylaminocarbonylamino or diethylaminocarbonylamino, C_{1-6}alkylaminocabonylC_{1-6}alkylamino, e.g. methylaminocarbonylmethylamino, aminothiocarbonylamino, C_{1-6}alkylaminothiocarbonylamino, e.g. methylaminothiocarbonylamino or ethylaminothiocarbonylamino, C_{1-6}dialkylaminothiocarbonylamino, e.g. dimethylaminothiocarbonylamino or diethylaminothiocarbonylamino, C_{1-6}alkylaminothiocarbonylC_{1-6}alkylamino, e.g. ethylaminothiocarbonylmethylamino, -CONHC(=NH)NH_2, C_{1-6}alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, C_{1-6}dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, optionally substituted phenylsulphonylamino, aminosulphonylamino (-$NHSO_2NH_2$), C_{1-6}alkylaminosulphonylamino, e.g. methylaminosulphonyl-amino or ethylaminosulphonylamino, C_{1-6}dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, optionally substituted morpholinesulphonylamino or morpholinesulphonylC_{1-6}alkylamino, optionally substituted phenylaminosulphonylamino, C_{1-6}alkanoylamino, e.g. acetylamino, aminoC_{1-6}alkanoylamino e.g. aminoacetylamino, C_{1-6}dialkylaminoC_{1-6}alkanoylamino, e.g. dimethylaminoacetylamino, C_{1-6}alkanoylaminoC_{1-6}alkyl, e.g. acetylaminomethyl, C_{1-6}alkanoylaminoC_{1-6}alkylamino, e.g. acetamidoethylamino, C_{1-6}alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino or optionally substituted benzyloxy, pyridylmethoxy, thiazolylmethoxy,

benzyloxycarbonylamino, benzyloxycarbonylaminoC_{1-6}alkyl e.g. benzyloxycarbonylaminoethyl, benzothio, pyridylmethylthio or thiazolylmethylthio groups.

Where desired, two R^{11} substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C_{1-6}alkylenedioxy group such as methylenedioxy or ethylenedioxy.

It will be appreciated that where two or more R^{11} substituents are present, these need not necessarily be the same atoms and/or groups. In general, the substituent(s) may be present at any available ring position in the aromatic or heteroaromatic group represented by R^7.

Alkyl groups represented by the groups R^2 or R^3 in compounds of the invention include for example straight or branched C_{1-6}alkyl groups such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl groups. Alkoxy groups represented by the groups R^2 or R^3 include straight or branched C_{1-6}alkoxy groups such as methoxy or ethoxy groups. Halogen atoms represented by the groups R^2 or R^3 include for example fluorine, chlorine, bromine or iodine atoms. When R^2 and/or R^3 is a haloalkyl or haloalkoxy group it may be for example a haloC_{1-6}alkyl or haloC_{1-6}alkoxy group containing one, two or three halogen atoms selected from fluorine, chlorine, bromine or iodine atoms. Particular examples of groups of this type include $-CF_3$, $-OCF_3$, $-CCl_3$, $-OCCl_3$, $-CHF_2$, $-OCHF_2$, $-CHCl_2$, $-OCHCl_2$, $-CH_2F$, $-OCH_2F$, $-CH_2Cl$ and $-OCH_2Cl$ groups.

The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and salts derived from inorganic and organic bases.

Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, alkylsulphonates, e.g. methanesulphonates, ethanesulphonates, or isethionates, arylsulphonates, e.g. p-toluenesulphonates, besylates or napsylates, phosphates, sulphates, hydrogen sulphates, acetates,

trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

Particularly useful salts of compounds according to the invention include pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

Generally in the compounds of the invention the group R is preferably a $-CO_2H$ group.

Alk^2 in compounds of formula (1) is preferably a $-CH_2-$ chain and m is preferably an integer 1.

R^4 and R^5 in compounds of the invention is each preferably a hydrogen atom.

In general in compounds of formula (1) $-Alk^1L^1-$ is preferably $-CH_2O-$ or $-CON(R^8)-$, particularly -CONH-.

The group R^1 in compounds of formula (1) is preferably an optionally substituted aromatic or heteroaromatic group. Particularly useful groups of these types include optionally substitued phenyl, pyridyl or pyrimidinyl groups.

Particularly useful classes of compounds according to the invention are those wherein R^6 is a group $-R^7$ [i.e. where t is zero] where R^7 is an optionally substituted heterocycloaliphatic, aromatic or heteroaromatic group as defined herein. Particularly useful groups of this type include optionally substituted C_{5-7}heterocycloaliphatic, especially optionally substituted pyrrolidinyl or thiazolidinyl, optionally substituted phenyl and optionally substituted C_{5-7}heteroaromatic, especially optionally substituted

pyridinyl groups. Optional substituents on these groups include in particular R^{11} atoms or groups where the group is an aromatic or heteroaromatic group and $-(L^3)_p(Alk^3)_qR^{10}$ groups as described earlier where the group is a nitrogen-containing heterocycloaliphatic group such as a pyrrolidinyl or thiazolidinyl group. Particularly useful $-(L^3)_p(Alk^3)_qR^{10}$ groups include those in which L^3 is a -CO-group. Alk^3 in these groups is preferably present (i.e. q is preferably an integer 1) and in particular is a $-CH_2-$ chain. Compounds of this type in which R^6 is a hydrogen atom or an optionally substituted aromatic or heteroaromatic group, especially an optionally substituted phenyl, pyridyl or imidazolyl group are particularly preferred.

Compounds according to the invention are potent and selective inhibitors of $\alpha 4$ integrins. The ability of the compounds to act in this way may be simply determined by employing tests such as those described in the Examples hereinafter.

The compounds are of use in modulating cell adhesion and in particular are of use in the prophylaxis and treatment of diseases or disorders involving inflammation in which the extravasation of leukocytes plays a role. The invention extends to such uses and to the use of the compounds for preparing a medicament for treating these diseases and disorders. Particular diseases or disorders of this type include inflammatory arthritis such as rheumatoid arthritis vasculitis or polydermatomyositis, multiple sclerosis, allograft rejection, diabetes, inflammatory dermatoses such as psoriasis or dermatitis, asthma and inflammatory bowel disease.

For the prophylaxis or treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) together with one or more pharmaceutically acceptable carriers, excipients or diluents.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration, or a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds for formula (1) may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

In addition to the formulations described above, the compounds of formula (1) may also be formulated as a depot preparation. Such long acting

formulations may be administered by implantation or by intramuscular injection.

For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

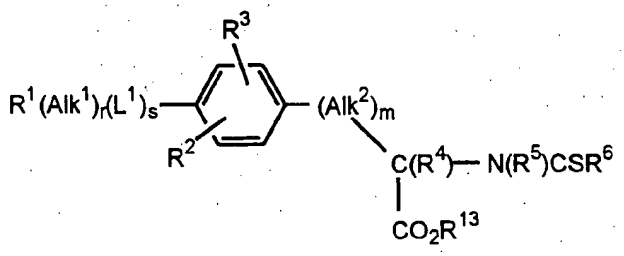
The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however, daily dosages may range from around 100ng/kg to 100mg/kg e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. In the following process description, the symbols R, R^1-R^6, L^1, Alk^1, Alk^2, m, r and s when used in the formulae depicted are to be understood to represent those groups described above in relation to formula (1) unless otherwise indicated. In the reactions described below, it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective

Groups in Organic Synthesis", John Wiley and Sons, 1991]. In some instances, deprotection may be the final step in the synthesis of a compound of formula (1) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups.

Thus according to a further aspect of the invention, a compound of formula (1) in which R is a $-CO_2H$ group may be obtained by hydrolysis of an ester of formula (2):

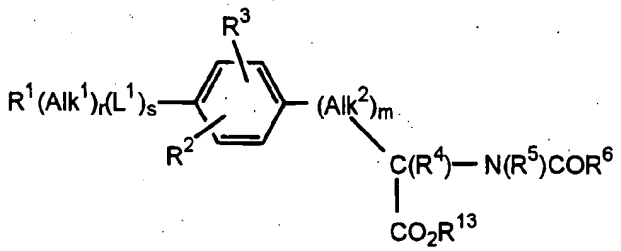


(2)

where R^{13} is an alkyl group.

The hydrolysis may be performed using either an acid or a base depending on the nature of R^{13}, for example an organic acid such as trifluoroacetic acid or an inorganic base such as lithium hydroxide optionally in an aqueous organic solvent such as an amide, e.g. a substituted amide such as dimethylformamide, an ether, e.g. a cyclic ether such as tetrahydrofuran or dioxane or an alcohol, e.g. methanol at around ambient temperature. Where desired, mixtures of such solvents may be used.

Intermediate esters of formula (2) may be prepared by treatment of a corresponding ester of formula (3):

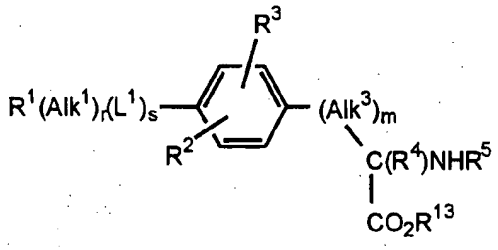


(3)

with a thiation reagent, such as Lawesson's Reagent, in an anhydrous solvent, for example a cyclic ether such as tetrahydrofuran, at an elevated temperature such as the reflux temperature.

This reaction may not be particularly suitable with starting materials in which other carbonyl groups are present, for example in L^1 and/or R^6, and which might undesirably participate in the reaction. To avoid this the reaction with the thiation reagent may be performed earlier in the synthesis of the compound of the invention with an intermediate in which other carbonyl groups are absent and any required carbonyl groups then subsequently introduced by for example acylation as generally described hereinafter.

Esters of formula (3) may be prepared by coupling an amine of formula (4):



(4)

or a salt thereof with an acid R^6CO_2H or an active derivative thereof. Active derivatives of acids include anhydrides, esters and halides.

The coupling reaction may be performed using standard conditions for reactions of this type. Thus for example the reaction may be carried out in a solvent, for example an inert organic solvent such as an amide, e.g. a

substituted amide such as dimethylformamide, an ether, e.g. a cyclic ether such as tetrahydrofuran, or a halogenated hydrocarbon, such as dichloromethane, at a low temperature, e.g. around -30°C to around ambient temperature, optionally in the presence of a base, e.g. an organic base such as an amine, e.g. triethylamine, pyridine, or dimethylaminopyridine, or a cyclic amine, such as N-methylmorpholine.

Where an acid R^6CO_2H is used, the reaction may additionally be performed in the presence of a condensing agent, for example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or N,N'-dicyclohexylcarbodiimide, advantageously in the presence of a catalyst such as a N-hydroxy compound e.g. a N-hydroxytriazole such as 1-hydroxybenzotriazole. Alternatively, the acid may be reacted with a chloroformate, for example ethylchloroformate, prior to reaction with the amine of formula (3).

The esters of formula (3) and acids R^6CO_2H are either known compounds or may be obtained from simpler compounds by one or more standard synthetic methods employing substitution, oxidation, reduction or cleavage reactions. Particular substitution approaches include conventional alkylation, arylation, heteroarylation, acylation, thioacylation, halogenation, sulphonylation, nitration, formylation and coupling procedures. It will be appreciated that these methods may also be used to modify the compounds of formula (1) and the esters or formula (2) where appropriate functional groups exist in these conmpounds.

Thus, for example compounds of the invention and intermediates thereto may be prepared by alkylation, arylation or heteroarylation. For example compounds containing a L^1H or L^3H group may be alkylated or arylated using a reagent $R^1(Alk^1)_rX$ or $R^{10}(Alk^3)_qX$ in which X is a leaving atom or group such as a halogen atom, e.g. a fluorine, bromine, iodine or chlorine atom or a sulphonyloxy group such as an alkylsulphonyloxy, e.g. trifluoromethylsulphonyloxy or arylsulphonyloxy, e.g. p-toluenesulphonyloxy group.

The alkylation or arylation reaction may be carried out in the presence of a base such as a carbonate, e.g. caesium or potassium carbonate, an alkoxide, e.g. potassium t-butoxide, or a hydride, e.g. sodium hydride, in a dipolar aprotic solvent such as an amide, e.g. a substituted amide such as dimethylformamide or an ether, e.g. a cyclic ether such as tetrahydrofuran.

In another example, compounds containing a L^1H or $-L^3H$ group may be functionalised by acylation or thioacylation, for example by reaction with a reagent $R^1(Alk^1)_rL^1X$ [wherein L^1 is a -C(O)-, -C(S)-, or $-N(R^8)C(S)-$ group], $R^{10}(Alk^3)_qCOX$ or $R^{10}(Alk^3)_qNHCOX$ in the presence of a base, such as a hydride, e.g. sodium hydride or an amine, e.g. triethylamine or N-methylmorpholine, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane or carbon tetrachloride or an amide, e.g. dimethylformamide, at for example ambient temperature, or by reaction with $R^1(Alk^1)_rCO_2H$ or $R^{10}(Alk^3)_qCO_2H$ or an activated derivative thereof, for example as described above for the preparation of esters of formula (3).

In a further example a compound may be obtained by sulphonylation of a compound where $R^1(Alk^1)_r(L^1)_s$ is an -OH group by reaction with a reagent $R^1(Alk^1)_rL^1Hal$ [in which L^1 is $-S(O)-$ or $-SO_2-$ and Hal is a halogen atom such as a chlorine atom] in the presence of a base, for example an inorganic base such as sodium hydride in a solvent such as an amide, e.g. a substituted amide such as dimethylformamide at for example ambient temperature.

In another example, a compound where $R^1(Alk^1)_r(L^1)_s$ is a $-L^1H$ group, may be coupled with a reagent R^1OH (where R^1 is other than a hydrogen atom) or R^1Alk^1OH in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl, diisopropyl- or dimethylazodicarboxylate to yield a compound containing a $R^1(Alk^1)_rO-$ group.

In a further example, ester groups $-CO_2Alk^5$ in the compounds may be converted to the corresponding acid [$-CO_2H$] by acid- or base-catalysed

hydrolysis depending on the nature of the group Alk^5 using the reactants and conditions described above for the hydrolysis of esters of formula (2).

In another example, $-OR^{12}$ groups [where R^{12} represents an alkyl group such as methyl group] in compounds of formula (1) may be cleaved to the corresponding alcohol -OH by reaction with boron tribromide in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane at a low temperature, e.g. around -78°C.

Alcohol [-OH] groups may also be obtained by hydrogenation of a corresponding $-OCH_2R^{12}$ group (where R^{12} is an aryl group) using a metal catalyst, for example palladium on a support such as carbon in a solvent such as ethanol in the presence of ammonium formate, cyclohexadiene or hydrogen, from around ambient to the reflux temperature. In another example, -OH groups may be generated from the corresponding ester [$-CO_2Alk^5$] or aldehyde [-CHO] by reduction, using for example a complex metal hydride such as lithium aluminium hydride or sodium borohydride in a solvent such as methanol.

Aminosulphonylamino [$-NHSO_2NH_2$] groups in the compounds may be obtained, in another example, by reaction of a corresponding amine [$-NH_2$] with sulphamide in the presence of an organic base such as pyridine at an elevated temperature, e.g. the reflux temperature.

In a further example amine ($-NH_2$) groups may be alkylated using a reductive alkylation process employing an aldehyde and a borohydride, for example sodium triacetoxyborohyride or sodium cyanoborohydride, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane, a ketone such as acetone, or an alcohol, e.g. ethanol, where necessary in the presence of an acid such as acetic acid at around ambient temperature.

In a further example, amine [$-NH_2$] groups in compounds of formula (1) may be obtained by hydrolysis from a corresponding imide by reaction with hydrazine in a solvent such as an alcohol, e.g. ethanol at ambient temperature.

In another example, a nitro [-NO_2] group may be reduced to an amine [-NH_2], for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as an ether, e.g. tetrahydrofuran or an alcohol e.g. methanol, or by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid.

Aromatic halogen substituents in the compounds may be subjected to halogen-metal exchange with a base, for example a lithium base such as n-butyl or t-butyl lithium, optionally at a low temperature, e.g. around -78°C, in a solvent such as tetrahydrofuran and then quenched with an electrophile to introduce a desired substituent. Thus, for example, a formyl group may be introduced by using dimethylformamide as the electrophile; a thiomethyl group may be introduced by using dimethyldisulphide as the electrophile.

In another example, sulphur atoms in the compounds, for example when present in a linker group L^1 or L^3 may be oxidised to the corresponding sulphoxide or sulphone using an oxidising agent such as a peroxy acid, e.g. 3-chloroperoxybenzoic acid, in an inert solvent such as a halogenated hydrocarbon, e.g. dichloromethane, at around ambient temperature.

N-oxides of compounds of formula (1) may be prepared for example by oxidation of the corresponding nitrogen base using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70°C to 80°C, or alternatively by reaction with a peracid such as peracetic acid in a solvent, e.g. dichloromethane, at ambient temperature.

Salts of compounds of formula (1) may be prepared by reaction of a compound of formula (1) with an appropriate base in a suit able solvent or mixture of solvents e.g. an organic solvent such as an ether e.g. diethylether, or an alcohol, e.g. ethanol using conventional procedures.

Where it is desired to obtain a particular enantiomer of a compound of formula (1) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers.

Thus for example diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (1) e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation and the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt.

In another resolution process a racemate of formula (1) may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above.

The following Examples illustrate the invention. All temperatures are in °C. The following abbreviations are used:

EDC - 1-(3-dimethylaminopropyl)3-ethycarbodiimide;
DMF - dimethylformamide;
DMSO - dimethylsulphoxide;
HOBT - 1-hydroxybenzotriazole;
THF - tetrahydrofuran;
TFA - trifluoroacetic acid;
NMM - N-methylmorpholine;
DCM - dichloromethane;
Ph - phenyl;
BOC - tert-butoxycarbonyl;
EtOAc - ethyl acetate;
MeOH - methanol;
LDA - lithium diisopropylamide
tyr - tyrosine;
Ar - aryl;
HetAr - heteroaryl;
pyr - pyridine;
thiopro - thioproline;
Bu - butyl
Me - methyl

INTERMEDIATE 1

***N*-BOC-*D*-thioproline-(*O*-2,6-dichlorobenzyl)-*L*-tyrosine methyl ester**

EDC (634mg, 3.3mmol) was added to a solution of *N*-BOC-*D*-thioproline (699mg, 3mmol), (*O*-2,6-dichlorobenzyl)-*L*-tyrosine methyl ester hydrochloride (1.17g, 3mmol), HOBT (446mg, 3.3mmol) and NMM (692µl,

6.3mmol) in DCM (30ml). The mixture was stirred for 4h at room temperature then diluted with DCM (20ml) and washed with dilute hydrochloric acid (1M, 50ml), saturated $NaHCO_3$ solution (50ml) and water (50ml). The DCM solution was dried (Na_2SO_4) and evaporated under reduced pressure to give the title compound (1.70g) as a white foam. δH (DMSO-d_6, 300K) 8.41 (1H, br s, CONH), 7.57-7.43 (3H, m, ArH), 7.15 (2H, d, J 8.5Hz, ArH), 6.96 (2H, d, J 8.6 Hz, ArH), 5.18 (2H, s, OCH_2Ar), 4.6-4.4 (2H, br m, CHαthiopro + CHαtyr), 4.56 (1H, d, J 8.9Hz, NCH_AH_BS), 4.23 (1H, d, J 9.0Hz, NCH_AH_BS), 3.64 (3H, s, CO_2Me), 3.19 (1H, dd, J 7.5, 11.5Hz, $CHCH_AH_BS$), 3.04 (1H, dd, J 5.1, 13.7Hz, $CHCH_AH_BAr$), 2.85 (1H, dd, J 9.6, 13.7Hz, $CHCH_AH_BAr$), 2.7 (1H, br m, $CHCH_AH_BS$) and 1.33 (9H, br s, tBu); m/z (ESI, 60V) 591 M^+ + Na).

INTERMEDIATE 2

Methyl (2R)-3-{4-[(2,6-dichlorobenzyl)oxy]phenyl}-2-({[(4S)-3-(tert-butoxycarbonyl)-1,3-thiazolan-4-yl]carbothioyl}amino)propanoate

Lawesson's reagent (202mg, 0.5mmol) was added to a solution of Intermediate 1 (569mg, 1mmol) in THF (10ml). The suspension was refluxed for 3.5h to give a yellow solution. The solvent was removed under reduced pressure and the residue purified by column chromatography (SiO_2; DCM) to give the title compound as a colourless gum (345mg, 59%). δH (DMSO-d_6, 300K) 10.3 (1H, br s, CSNH), 7.57-7.42 (3H, m, ArH), 7.17 (2H, d, J 8.3Hz, ArH), 6.96 (2H, d, J 8.6Hz, ArH), 5.27 (1H, br s, CHαthiapro), 5.18 (2H, s, OCH_2Ar), 4.88 (1H, br s, CHαtyr), 4.65 (1H, d, J 9.1Hz, NCH_AH_BS) 4.37 (1H, d, J 9.2Hz, NCH_AH_BS), 3.66 (3H, s, CO_2Me), 3.33-3.27 (1H, m, $CHCH_AH_BS$), 3.18 (1H., dd, J 5.5, 14.0Hz, $CHCH_AH_BAr$), 3.05 (1H, dd, J 9.1, 14.0Hz, $CHCH_AH_BAr$), 2.73 (1H, br m, $CHCH_AH_BS$) and 1.31 (9H, br s, CMe_3); m/z (ESI, 60V) 605 (M^+Na).

INTERMEDIATE 3

Methyl (2R)-3-{4-[(2,6-dichlorobenzyl)oxy]phenyl}-2-{[(4S)-1,3-thiazolan-4-ylcarbothioyl]amino}propanoate hydrochloride

Anhydrous HCl gas was bubbled through a solution of Intermediate 2 (324mg, 0.554mmol) in EtOAc (10ml) for one minute. After 30min the solvent was removed under reduced pressure to give the title compound

(292mg) as a yellow solid. δH (DMSO-d_6, 300K) 11.19 (1H, br d, J 7.3Hz, CSNH), 7.57-7.43 (3H, m, ArH), 7.20 (2H, d, J 8.6Hz, ArH), 6.98 (2H, d, J 8.6Hz, ArH), 5.21-5.18 (1H, m, CHαtyr), 5.18 (2H, s, OCH_2Ar), 4.65 (1H, br t, J 7.7Hz, CHαthiopra), 4.33 (1H, d, J 9.6Hz, NCH_AH_BS), 4.28 (1H, d, J 9.6Hz, NCH_AH_BS), 3.69 (3H, s, CO_2Me), 3.33 (1H, dd, J 7.1, 11.2Hz, $CHCH_AH_BS$), 3.23 (1H, dd, J 5.2, 13.9Hz, CH_AH_BAr), 3.08 (1H, dd, J 9.8, 13.9Hz, CH_AH_BAr) and 2.61 (1H, dd, J 8.5, 11.2Hz, $CHCH_AH_BS$); m/z (ESI, 60V) 485 (M^++1).

INTERMEDIATE 4

Methyl (2R)-2-({[(4S)-3-acetyl-1,3-thiazolan-4-yl]carbothioyl}amino)-3-{4-[(2,6-dichlorobenzyl)oxy]phenyl}propanoate

Acetic anhydride (57μl, 0.602mmol) was added to a solution of Intermediate 3 (285mg, 0.547mmol) and NMM (60μl, 0.547mmol) in DCHM(10ml). The mixture was stirred at room temperature for 3h, diluted with DCM (100ml), washed with dilute HCl (aqueous) (20ml), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2; EtOAc/hexane, 50:50 to 75:25) to give the title compound as a colourless oil (285mg). δH (DMSO-d_6, 400K) 9.67 (1H, br s, CSNH), 7.51-7.39 (3H, m, ArH), 7.17 (2H, d, J 8.6Hz, ArH), 6.97 (2H, d, J 8.6Hz, ArH), 5.36 (1H, dd, J 5.8, 8.1Hz, CHαtyr), 5.26 (2H, s, OCH_2Ar), 5.15 (1H, dd, J 4.6, 7.4Hz, CHαthiopro), 4.83 (1H, d, J 9.3Hz, NCH_AH_BS), 4.51 (1H, d, J 9.3Hz, NCH_AH_BS), 3.68 (3H, s, CO_2Me), 3.39 (1H, dd, J 7.5, 11.7Hz, $CHCH_AH_BS$), 3.21 (1H, dd, J 5.8, 14.2Hz, CH_AH_BAr), 3.13 (1H, dd, J 8.3, 14.2Hz, CH_AH_BAr), 3.07 (1H, dd, J 4.8, 11.7Hz, $CHCH_AH_BS$) and 1.95 (3H, s, $NCOCH_3$); m/z (ESI, 60V) 527 (M^++1).

EXAMPLE 1

(A) **(2R)-2-({[(4S)-3-Acetyl-1,3-thiazolan-4-yl]carbothioyl}amino)-3-{4-[(2,6-dichlorobenzyl)oxy]phenyl}propanoic acid**

(B) **(2R)-2-({[(4R)-3-Acetyl-1,3-thiazolan-4-yl]carbothioyl}amino)-3-{4-[(2,6-dichlorobenzyl)oxy]phenyl}propanoic acid**

Lithium hydroxide monohydrate (25mg, 0.58mmol) was added to a solution of Intermediate 4 (280mg, 0.531mmol) in THF (5ml) and water (5ml). After 1h at room temperature the THF was removed under reduced

pressure, the aqueous residue acidified and extracted with DCM (2 x 50ml). The extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give a fluffy white solid (233mg). Separation by preparative HPLC gave the title compound, diastereoisomer A. δH (DMSO-d_6, 390K) 955 (1H, br s, CSNH), 7.51-7.39 (3H, m, ArH), 7.17 (2H, d, J 8.7Hz, ArH), 6.96 (2H, d, J 8.7ArH), 5.26 (2H, s, OCH_2Ar), 5.26-5.22 (1H, m, CHαtyr), 5.15 (1H, dd, J 4.8, 7.4Hz, CHαthiapro), 4.84 (1H, d, J 9.3Hz, NCH_AH_BS), 4.50 (1H, d, J 9.3Hz, NCH_AH_BS), 3.38 (1H. dd J 7.5, 11.7Hz, $CHCH_AH_BS$) 3.25 (1H, dd, J 5.4, 14.3Hz, CH_AH_BAr), 3.06 (1H, dd, J 4.7, 11.7Hz, $CHCH_AH_BS$), and 1.94 (3H, s, $NCOCH_3$); m/z (ESI, 60V), 513 (M^++1). and the title compound, diastereoisomer B δH (DMSO-d_6, 390K) 9.49 (1H, br s, CSHN) 7.51-7.39 (3H, m, ArH), 7.20 (2H, d, J 8.6Hz, ArH), 6.95 (2H, d, J 8.6Hz, ArH), 5.30-5.25 (1H, m, CHαtyr), 5.25 (2H, s, OCH_2Ar), 5.16 (1H, dd, J 4.3, 7.5Hz, CHαthiopro), 4.81 (1H, d, J 9.4Hz, NCH_AH_BS), 4.46 (1H, d, J 9.4Hz, NCH_AH_BS), 3.45 (1H, dd, J 7.5, 11.7Hz, $CHCH_AH_BS$), 3.26 (1H, dd, J 5.5, 14.3Hz, CH_AH_BAr), 3.20-3.10 (2H, m, CH_AH_BAr + $CHCH_AH_BS$) and 1.93 (3H, s, $NCOCH_3$); m/z (ESI, 60V) 513 (M^++1).

The following assays can be used to demonstrate the potency and selectivity of the compounds according to the invention. In each of these assays an IC_{50} value was determined for each test compound and represents the concentration of compound necessary to achieve 50% inhibition of cell adhesion where 100% = adhesion assessed in the absence of the test compound and 0% = absorbance in wells that did not receive cells.

$\alpha_4\beta_1$ Integrin-dependent Jurkat cell adhesion to VCAM-Ig

96 well NUNC plates were coated with $F(ab)_2$ fragment goat anti-human IgG Fcγ-specific antibody [Jackson Immuno Research 109-006-098: 100 µl at 2 µg/ml in 0.1M $NaHCO_3$, pH 8.4], overnight at 4°. The plates were washed (3x) in phosphate-buffered saline (PBS) and then blocked for 1h in PBS/1% BSA at room temperature on a rocking platform. After washing (3x in PBS) 9 ng/ml of purified 2d VCAM-Ig diluted in PBS/1% BSA was added and the plates left for 60 minutes at room temperature on a rocking platform. The plates were washed (3x in PBS) and the assay then

performed at 37° for 30 min in a total volume of 200 µl containing 2.5 x 10^5 Jurkat cells in the presence or absence of titrated test compounds.

Each plate was washed (2x) with medium and the adherent cells were fixed with 100µl methanol for 10 minutes followed by another wash. 100µl 0.25% Rose Bengal (Sigma R4507) in PBS was added for 5 minutes at room temperature and the plates washed (3x) in PBS. 100µl 50% (v/v) ethanol in PBS was added and the plates left for 60min after which the absorbance (570nm) was measured.

$\alpha_4\beta_7$ Integrin-dependent JY cell adhesion to MAdCAM-Ig

This assay was performed in the same manner as the $\alpha_4\beta_1$ assay except that MAdCAM-Ig (150ng/ml) was used in place of 2d VCAM-Ig and a sub-line of the β-lympho blastoid cell-line JY was used in place of Jurkat cells. The IC_{50} value for each test compound was determined as described in the $\alpha_4\beta_1$ integrin assay.

$\alpha_5\beta_1$ Integrin-dependent K562 cell adhesion to fibronectin

96 well tissue culture plates were coated with human plasma fibronectin (Sigma F0895) at 5µg/ml in phosphate-buffered saline (PBS) for 2 hr at 37°C. The plates were washed (3x in PBS) and then blocked for 1h in 100µl PBS/1% BSA at room temperature on a rocking platform. The blocked plates were washed (3x in PBS) and the assay then performed at 37°C in a total volume of 200µl containing 2.5x 10^5 K562 cells, phorbol-12-myristate-13-acetate at 10ng/ml, and in the presence or absence of titrated test compounds. Incubation time was 30 minutes. Each plate was fixed and stained as described in the $\alpha_4\beta_1$ assay above.

$\alpha_m\beta_2$-dependent human polymorphonuclear neutrophils adhesion to plastic

96 well tissue culture plates were coated with RPMI 1640/10% FCS for 2h at 37°C. 2 x 10^5 freshly isolated human venous polymorphonuclear neutrophils (PMN) were added to the wells in a total volume of 200µl in the presence of 10ng/ml phorbol-12-myristate-13-acetate, and in the presence or absence of test compounds, and incubated for 20min at 37°C followed by 30min at room temperature. The plates were washed in medium and

100µl 0.1% (w/v) HMB (hexadecyl trimethyl ammonium bromide, Sigma H5882) in 0.05M potassium phosphate buffer, pH 6.0 added to each well. The plates were then left on a rocker at room temperature for 60 min. Endogenous peroxidase activity was then assessed using tetramethyl benzidine (TMB) as follows: PMN lysate samples mixed with 0.22% H_2O_2 (Sigma) and 50µg/ml TMB (Boehringer Mannheim) in 0.1M sodium acetate/citrate buffer, pH 6.0 and absorbance measured at 630nm.

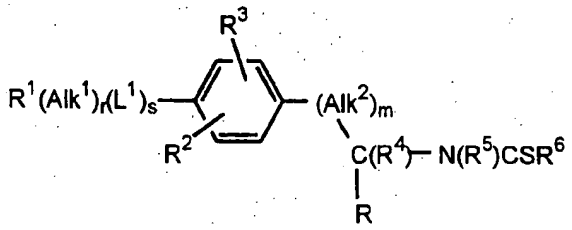
αIIb/β_3 -dependent human platelet aggregation

Human platelet aggregation was assessed using impedance aggregation on the Chronolog Whole Blood Lumiaggregometer. Human platelet-rich plasma (PRP) was obtained by spinning fresh human venous blood anticoagulated with 0.38% (v/v) tri-sodium citrate at 220xg for 10 min and diluted to a cell density of 6 x 10^8/ml in autologous plasma. Cuvettes contained equal volumes of PRP and filtered Tyrode's buffer (g/liter: NaCl 8.0; $MgCl_2.H_2O$ 0.427; $CaCl_2$ 0.2; KCl 0.2; D-glucose 1.0; $NaHCO_3$ 1.0; $NaHPO_4.2H_2O$ 0.065). Aggregation was monitored following addition of 2.5µM ADP (Sigma) in the presence or absence of inhibitors.

In the above assays the compounds of the invention generally have IC_{50} values in the $\alpha_4\beta_1$ and $\alpha_4\beta_7$ assays of 1 µM and below. In the other assays featuring α integrins of other subgroups the same compounds had IC_{50} values of 50µM and above thus demonstrating the potency and selectivity of their action against α_4 integrins.

CLAIMS

1. A compound of formula (1):



(1)

wherein

R^1 is a hydrogen atom or an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;

Alk^1 is an optionally substituted aliphatic or heteroaliphatic chain;

L^1 is a linker atom or group;

r and s is each zero or an integer 1;

R^2 and R^3, which may be the same or different, is each a hydrogen or halogen atom or a straight or branched alkyl, haloalkyl, alkoxy, haloalkoxy, hydroxyl or nitro group;

Alk^2 is a straight or branched alkylene chain;

m is zero or an integer 1;

R^4 is a hydrogen atom or a methyl group;

R^5 is a hydrogen atom or a straight or branched alkyl group;

R^6 is a group $-(CH_2)_tR^7$ in which t is zero or the integer 1 and R^7 is an optionally substituted polycycloaliphatic, heterocycloaliphatic, polyhetero-cycloaliphatic, aromatic or heteroaromatic group;

R is a carboxylic acid ($-CO_2H$) or a derivative thereof;

and the salts, solvates and hydrates thereof.

2. A compound according to Claim 1 wherein R is a $-CO_2H$ group.

3. A compound according to Claim 1 or Claim 2 wherein Alk is a $-CH_2-$ chain and m is an integer 1.

4. A compound according to Claim 1 to Claim 3 wherein R^4 and R^5 is each a hydrogen atom.

5. A compound according to Claim 1 to Claim 4 wherein $-Alk^1L^1-$ is a $-CH_2O-$ or $-CON(R^8)-$ group where R^8 is a hydrogen atom or a straight or branched alkyl group.

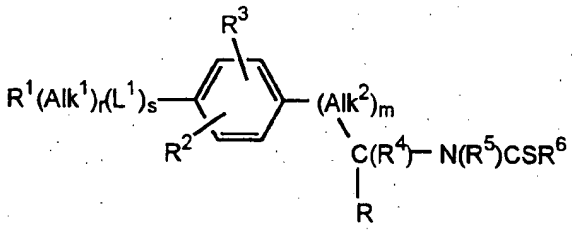
6. A compound according to Claim 1 to Claim 5 wherein R^1 is an optionally substituted aromatic or heteroaromatic group.

7. A compound according to Claim 6 wherein R^1 is an optionally substituted phenyl, pyridyl or pyrimidinyl group.

8. A compound according to any one of Claim 1 to Claim 7 wherein R^6 is an optionally substituted heterocycloaliphatic, aromatic or heteroaromatic group.

9. A compound according to Claim 8 wherein R^6 is an optionally substituted pyrrolidinyl, thiazolidinyl, phenyl or pyridyl group.

10. A pharmaceutical composition comprising a compound of formula (1):



(1)

wherein

R^1 is a hydrogen atom or an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;

Alk^1 is an optionally substituted aliphatic or heteroaliphatic chain;

L^1 is a linker atom or group;

r and s is each zero or an integer 1;

R^2 and R^3, which may be the same or different, is each a hydrogen or halogen atom or a straight or branched alkyl, haloalkyl, alkoxy, haloalkoxy, hydroxyl or nitro group;

Alk^2 is a straight or branched alkylene chain;

m is zero or an integer 1;

R^4 is a hydrogen atom or a methyl group;

R^5 is a hydrogen atom or a straight or branched alkyl group;

R^6 is a group $-(CH_2)_tR^7$ in which t is zero or the integer 1 and R^7 is an optionally substituted polycycloaliphatic, heterocycloaliphatic, polyhetero-cycloaliphatic, aromatic or heteroaromatic group;

R is a carboxylic acid ($-CO_2H$) or a derivative thereof;

and the salts, solvates and hydrates thereof; together with one or more pharmaceutically acceptable carriers, excipients or diluents..

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/GB 99/00920

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D277/06 A61K31/425

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BACH E ET AL: "Anomalous optical rotation and circular dichroism of N-thioacylated.alpha.-amino acids and deriva" ACTA CHEM. SCAND. , vol. 20, no. 10, 1966, pages 2781-2794, XP002109904 see page 2783; table 1, the compounds of formula no. V --- -/--	1-4,8,9

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 July 1999	13.08.99
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Fink, D

2

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BARRETT G C: "Circular dichroism of N-thiobenzoyl-l-.alpha.-amino-acids. III. Their circular dichroism through the near-ultraviolet wavelength range" J. CHEM. SOC. C , no. 1, 1967, pages 1-5, XP002109905 see page 4; the table, see the first 5 compounds (and their cyclohexylammonium salts) beneath the heading: "alpha-Amino-acids (aromatic)" ---	1-4,8,9
X	JEPSON J B ET AL: "Reactions of alpha-Thioacylamino-acids. Their conversion into Thiazolones and Derivatives Thereof." J. CHEM. SOC.,1955, pages 1791-1797, XP002109906 see page 1794; table 1, see the entries 5-7 ---	1-4,8,9
X	TSUNEMATSU H ET AL: "Hydrolysis of phenylthiazolones of p-guanidinophenylalanine and arginine by trypsin and related enzymes" J. BIOCHEM. , vol. 94, no. 4, 1983, pages 1119-1125, XP002109907 see page 1122; scheme 1, the N-thiobenzoyl-L-amino acid wherein R = -CH2-C6H4-NH-C(=NH)-NH2 ---	1-4,8,9
X	HARTKE K ET AL: "Dithio and thiono esters. Part 61. Synthesis of.alpha.-amino dithioesters and endothiodipeptides" J. PRAKT. CHEM./CHEM.-ZTG. , vol. 338, no. 3, 1996, pages 251-256, XP002109908 see page 252, the general formula 7; and page 256, table 2, the compound no. 7o ---	1-4,8,9
X	DATABASE CROSSFIRE 'Online! Beilstein Informationssysteme GmbH, Frankfurt DE XP002109909 see the compound with the Beilstein Registry Number: 3161750 & CORNFORTH: CHEM. PENICILLIN,1949, page 688, 799 and 800 Princeton Book Review --- -/--	1-4

INTERNATIONAL SEARCH REPORT

Inte. onal Application No
PCT/GB 99/00920

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 015, no. 345 (C-0864), 3 September 1991 (1991-09-03) -& JP 03 135962 A (SHIKOKU CHEM CORP), 10 June 1991 (1991-06-10) abstract	1-4,8
A	WO 97 36859 A (RICO JOSEPH G ;SEARLE & CO (US); YU STELLA S (US); CHEN BARBARA B) 9 October 1997 (1997-10-09) page 287 - page 292; claim 1 page 120; example 47 page 31, line 4 - line 26	1-10
A	DE 196 54 483 A (MERCK PATENT GMBH) 2 January 1998 (1998-01-02) page 20 - page 21; claim 1 page 2, line 44 - line 50 page 3, line 33 - line 40	1-10
P,X	WO 99 06436 A (LOMBARDO LOUIS JOHN ;SEMKO CHRISTOPHER M (US); THORSETT EUGENE D () 11 February 1999 (1999-02-11) page 156; claim 1 pages 144-145; table II, the examples no. 86 and 91 examples 86,91; table II	1-4,8-10
P,X	WO 99 06437 A (SEMKO CHRISTOPHER M ;THORSETT EUGENE D (US); KREFT ANTHONY (US); A) 11 February 1999 (1999-02-11) page 235 - page 247; claim 1	1-10

2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/00920

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-10 (in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-10 (in part)

Present claim 1 relates to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Moreover, the expression "...or a derivative thereof..." (cf. the definition of the substituent group R in the present claim 1) is considered to be unclear in the sense of Article 6 PCT since this term is non-limiting as regards the structure of the compound of formula (1).

Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of the present formula (1) wherein m = 1 and Alk2 is a -CH2- chain, and wherein R is a carboxylic acid (-COOH) group.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter ɔnal Application No
PCT/GB 99/00920

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 03135962 A	10-06-1991	JP 2098990 C	22-10-1996
		JP 7121917 B	25-12-1995
WO 9736859 A	09-10-1997	AU 2536097 A	22-10-1997
		EP 0891325 A	20-01-1999
DE 19654483 A	02-01-1998	AU 3343097 A	21-01-1998
		CZ 9804249 A	17-03-1999
		WO 9800395 A	08-01-1998
		EP 0907637 A	14-04-1999
		NO 986090 A	23-12-1998
WO 9906436 A	11-02-1999	AU 8585198 A	22-02-1999
WO 9906437 A	11-02-1999	AU 8823498 A	22-02-1999